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Synthesis, theoretical calculation and α-glucosidase inhibition of new chalcone oximes

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Abstract: A series of eleven hydroxy and methoxy substituted new chalcone oximes (**2a-2k**) were synthesized by the condensation of chalcone (**1a-1k**) with hydroxylamine hydrochloride in pyridine. Structures of the synthesized compounds were characterized using NMR (1D; ^{1}H, ^{13}C/APT and 2D ^{1}H-^{1}H COSY, NOESY and ROESY), FT-IR, UV, LC-MS spectral data and elemental analysis. These synthetic compounds (**2a-k**) were screened for their α-glucosidase inhibition. The most *α*-glucosidase inhibitory activity were observe on compounds **2a** and **2b** with in the range of 1.61-3.36 µM (IC_{50} values) which were more active then acarbose (IC_{50}, 13,34 µM). IC_{50} values of other synthesized compounds **2c-2h** are within the range of 7,25-25,55 µM which were more or as active as acarbose, but, IC_{50} values for compounds **2j-2k** were not observed. The geometric isomers of compounds **2a-2k** were calculated theoretically. Experimental and theoretical calculations showed that *cisoid* 1*E*,2*E* is the most stable geometrical isomer of all.

Keywords: Chalcone; chalcone oxime; *α*-glucosidase inhibition.

1. Introduction

α-Glucosidase has a crucial role for the biosynthesis of glycoproteins and digestion of carbohydrates.[1] Inhibition of enzyme plays an important role for the treatment of degenerative diseases. Some of α-glucosidase inhibitors (Acarbose, Miglitol, and Voglibose) have been used as drugs by diabetic patients.[2] *α*- and *β*-glucosidases were known to catalyze the hydrolysis of the glycosidic bonds involving a terminal glucose at the cleavage site and they were most extensively studied.[3] Acarbose was the first member of α-glucosidase inhibitors approved for the treatment of type II diabetes[4]. A number of *α*-glucosidase inhibitors discovered recently and reviewed in an extensive fashion.[5-7]

Chalcones are medicinally important group of naturally occurring bioactive compounds. Chalcones and their analogues can be prepared by Claisen−Schmidt reaction and are well known intermediates for synthesizing various heterocyclic compounds. Chalcone possess various biological activities such as anti-tubercular,[8-9] anti-inflammatory,[10] antioxidant,[11] antileishmanial,[12] anti-malarial,[13-14] and antimicrobial.[15-16] Since a broad spectrum of biological activities are associated with the natural or analogous chalcone compounds, and also its derivatives chalcone oximes and chalcone

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Schiff bases have been reported to exhibit various antimicrobial[15-16] and tyrosinase inhibitory activities,[17-18] respectively. As mentioned, many of the chalcone oxime compounds showed potent biological activities and low toxicities.[19] Some of the chalcone oxime compounds have been used as clinical medical agents, thus, it was considered worthwhile to synthesize and evaluate a new series of chalcone oximes for their biological activity. The present study is devoted to the synthesis new hydroxy/methoxy substituted chalcone oximes (**2a-2k**) by the condensation of chalcones (**1a-1k**) with hydroxylamine hydrochloride in the pyridine and to test their *α*-glucosidase inhibition activity and to find out the most stable geometric isomers of compounds **2a-2k** by theoretical calculation. The synthesis of chalcone oxime starting form chalcone may have four possible geometric isomers. Theoretical calculations were performed with HYPERCHEM 7.5 program to determine the most stable geometric isomer of compounds **2a-2k**.[20-22] The compounds **2g** and **2j** had mentioned as an stereoisomer products with 1*Z*,2*E* geometry in the literature with highly different melting points,[23] but, in our case, geometry of double bonds for compounds **2g** and **2j** were found to be 1*E*,2*E* geometry.

2. Experimental

2.1. Materials and Apparatus

All chemical reagents used in the synthesis were high grade of commercial products purchased from Sigma, Fluka or Aldrich and used without further purification. The solvents (*n*-hexane, ethyl acetate, chloroform, diethyl ether, pyridine, methanol) used were either analytical grade or bulk solvents distilled before use. Thin-layer chromatography (TLC) and column chromatography were carried out on Merck precoated 60 Kieselgel F_{254} analytical aluminum acidic plates and silica gel 60 (0.040-0.063 mm), respectively. Melting points were determined using Thermo-var apparatus fitted with a microscope and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400/100 MHz NMR with tetramethylsilane (TMS) as an internal standard, respectively. UV-Vis absorbance measurements and spectral analyses were carried out on a Unicam UV2-100 at 25 ^{o}C. Infrared spectra were obtained with a Perkin-Elmer 1600 FT-IR (4000-400 cm^{-1}) spectrometer. The mass spectral analyses were carried out on a Micromass Quattro LC-MS spectrophotometer. The elemental analyses were performed on a Costech ESC 4010 instrument.

2.2. Methods

The known chalcones[19,24-31] (**1a-1k**) were synthesized according to the literature.[32-33]

*2.2.1. General procedure for the synthesis of chalcone oximes **2a-2k**:*

Hydroxylamine hydrochloride (0.01 mol) in water (5 mL) was added to a solution of compound **1a-1k** (0.01 mol) which were synthesized according to the literature in pyridine (10 mL).[23,34-37] The reaction mixture was refluxed for 3 h with constant stirring and checked by TLC on silica gel plate. After the completion, the reaction mixture was cooled, acidified with diluted acetic acid, evaporated and purified with column chromatography using; hexane 50 mL, *n*-hexane-ethyl acetate (4:1, 50 mL; 4:2, 50 mL; 1:1, 100 mL) solvent system, respectively, to give compounds **2a-2k**.

*(1E,2E)-1-(3-hydroxyphenyl)-3-phenylprop-2-en-1-one oxime (**2a**):* Yield: 67%, white solid, R_f = 0.67 (*n*-hexane-diethyl ether, 1:3); m.p.(^{o}C): 160-163, UV-vis λ nm (logϵ): 281.86 (2.01), IR (KBr, cm^{-1}): 3262, 3163 (-OH, =NOH), 1602 (-C=N), 1594 (-C=C-olefinic), 1574, 1446 (-C=C- aromatic), ^{1}H-NMR (400 MHz, DMSO-d_6): 6.77 (d, *J*: 16.0 Hz, 1H, α-H), 7.72 (d, *J*: 16.0 Hz, 1H, β-H), ar-H: [7.49-7.46 (m, 2H), 7.37-7.25 (m, 5H), 6.79-6.75 (m, 2H)],^{13}C-NMR (100 MHz, DMSO-d_6):157.17 (-C=NOH), 115.66 (α-C), 138.55 (β-C), ar-C [157.09 (C), 136.43 (C), 136.30 (C), 129.08 (CH), 128.75 (CH), 128.50 (2CH), 126.98 (2CH), 120.22 (CH), 116.95 (CH), 115.81 (CH), Anal. calcd for $C_{15}H_{13}NO_2$ (m.w.: 239): C, 75.30; H, 5.48; N, 5.85. Found: C, 75.43; H, 5.56; N, 5.95. LC-MS: (*m/z*) (%) $[M\text{-}OH+1]^{+}$: 223(100).

*(1E,2E)-1-(4-hydroxyphenyl)-3-phenylprop-2-en-1-one oxime (**2b**)*: Yield: 69%, white solid, R_f = 0.64 (*n*-hexane -diethyl ether, 1:3), m.p.(°C): 156-159, UV-vis λ nm (logϵ): 280.86 (1.25), IR (KBr, cm^{-1}): 3268, 3163 (-OH, =NOH), 1608 (-C=N), 1594 (-C=C-olefinic), 1575, 1445 (-C=C-aromatic), ^{1}H-NMR (400 MHz, DMSO-d_6): 6.79 (d, *J*: 16. 8 Hz, 1H, α-H), 7.62 (d, *J*: 16.8 Hz, 1H, β-H), 11.44 (s, 1H, =NOH), 9.75 (s, 1H, -OH), ar-H: [6.90-6.89 (m, 2H), (7.42-7.35 (m, 7H)], ^{13}C-NMR (100 MHz, DMSO-d_6): 157.98 (-C=NOH), 117.56 (α-C), 138.89 (β-C), ar-C [157.58 (C), 136.31 (C), 130.44 (2CH), 128.81 (CH), 128.54 (2CH), 127.18 (2CH), 126.19 (C), 114.97 (2CH)]. Anal. calcd for $C_{15}H_{13}NO_2$ (m.w.: 239): C, 75.30; H, 5.48; N, 5.85, Found: 75.48; H, 5.59; N, 5.75. LC-MS: (*m/z*) (%) $[M+Na+H_2O]^+$: 280(100).

*(1E,2E)-1,3-bis(2-methoxyphenyl)prop-2-en-1-one oxime (**2c**)*: Yield: 76%, white solid, R_f=0.51 (*n*-hexane -diethyl ether, 1:3), m.p.(°C): 126-128, UV-vis λ nm (logϵ): 283.45 (1,29), 343.77 (0.80), IR (KBr, cm^{-1}): 3165 (=NOH), 1606 (-C=N), 1593 (-C=C-olefinic), 1487, 1433 (-C=C-aromatic), ^{1}H-NMR (400 MHz, DMSO-d_6): 11.31 (s, 1H, =NOH), 6.74 (d, *J*: 16.4 Hz, 1H, α-H), 7.76 (d, *J*: 16.4 Hz, 1H, β-H), ar-H: [7.61-7.59 (m, 2H), 7.40-7.19 (m, 4H), 7.05-6.92 (m, 2H)], 3,69, 3,68 (s, 6H, -OCH_3,), ^{13}C-NMR (100 MHz, DMSO-d_6): 163.96 (-C=NOH), 120.79 (α-C), 138.67 (β-C), ar-C [161.21(C), 157.45 (C), 131.41 (CH), 130.20 (CH), 127.87 (CH), 127.92 (CH), 120.66 (C), 120.54 (C), 126.09 (CH), 120.66 (CH), 117.35 (CH), 110.97 (CH)], 55.70, 55.48 [-OCH_3]. Anal. calcd for $C_{17}H_{17}NO_3$ (m.w.: 283): C, 72.07; H, 6.05; N, 4.94. Found: C, 72.08; H, 6.14; N, 4.91. LC-MS: (*m/z*) (%) $[M-OH]^+$: 266 (100), $[M+H]^+$: 284(80).

*(1E,2E)-3-(2,3-dimethoxyphenyl)-1-(2-methoxyphenyl)prop-2-en-1-one oxime (**2d**)*: Yield: 81%, white solid, R_f =0.54 (*n*-hexane -diethyl ether, 1:3), m.p.(°C): 121-123, UV-vis λ nm (logϵ): 304.14 (1.41), IR (KBr, cm^{-1}): 3184 (=NOH), 1599 (-C=N), 1581 (-C=C-olefinic), 1593, 1433 (-C=C-aromatic), ^{1}H-NMR (400 MHz, DMSO-d_6): 11.42 (s, 1H, =NOH), 6.61 (d, *J*: 16.8 Hz, 1H, α-H), 7.62 (d, *J*: 16.8 Hz, 1H, β-H), ar-H: [7.43-7.47 (m, 1H), 7.19-7.25 (m, 2H), 6.99-6.14 (m, 4H)], 3.77, 3.52, 3.50 (s, 9H, -OCH_3,),^{13}C-NMR (100 MHz, DMSO-d_6):157.94 (-C=NOH), 118.19 (α-C), 131.45 (β-C), ar-C [153.18 (C), 154.88 (C), 147.31 (C), 130.67 (CH), 130.40 (CH), 130.37 (C), 124.92 (CH), 124.76 (C), 120.79 (CH), 118.19 (CH), 113.57 (CH), 111.83 (CH)], 60.94, 56.14, 55.83 [-OCH_3]. Anal. calcd for: $C_{18}H_{19}NO_4$ (m.w.: 313): C, 68.99; H, 6.11; N, 4.47. Found: C, 68.82; H 6.21; N 4.43. LC-MS : (*m/z*) (%) $[M+Na]^+$: 336(100).

*(1E,2E)-1-(2-methoxyphenyl)-3-(2,3,4-trimethoxyphenyl)prop-2-en-1-one oxime (**2e**)*: Yield: 80%, white solid, R_f =0.61 (*n*-hexane/diethyl ether, 1:3), m.p.(°C): 154-156, UV-vis λ nm (logϵ): 304.28 (1.53), IR (KBr, cm^{-1}): 3178 (=NOH), 1598 (-C=N), 1584 (-C=C-olefinic), 1433 (-C=C-aromatic), ^{1}H-NMR (400 MHz, DMSO-d_6): 11.02 (s, 1H, =NOH), 6.62 (d, *J*: 16.8 Hz, 1H, αCH), 7.67 (d, *J*: 16.8 Hz, 1H, βCH), ar-H: [7.43-7.47 (m, 2H), 7.11-7.04 (m, 2H), 6.78-6.69 (m, 2H)], 3.91, 3.84, 3.74, 3.72 (s, 12H, -OCH_3,),^{13}C-NMR (100 MHz, DMSO-d_6): 157.98 (-C=NOH), 120.79 (αCH), 135.98 (βCH), ar-C [156.56 (C), 155.57 (C), 154.48 (C), 133.32 (CH), 136.57 (C), 129.80 (CH), 124.68 (C), 122.26 (C), 128.55 (CH), 127.25 (CH), 117.57 (CH), 112.08 (CH)], 61.31, 60.93, 56.21, 56.03, 55.83 [-OCH_3]. Anal. calcd for $C_{19}H_{21}NO_5$ (m.w.: 343): C, 66.46; H, 6.16; N, 4.08. Found: C, 66.57; H, 6.21; N, 4.03. LC-MS: (*m/z*) (%) $[M+1]^+$: 344 (100), $[M+Na]^+$: 366 (75).

*(1E,2E)-3-(2-methoxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one oxime (**2f**)*: Yield: 72%, white solid, R_f = 0.57 (*n*-hexane-diethyl ether, 1:3), m.p.(°C): 134-135, UV-vis λ nm (logϵ): 279.27 (1.50), 321.30 (1.04), IR (KBr, cm^{-1}): 3162 (=NOH), 1608 (-C=N), 1594 (-C=C-olefinic), 1577, 1447(-C=C-aromatic), ^{1}H-NMR (400 MHz, DMSO-d_6): 11.51 (s, 1H, =NOH), 6.90 (d, *J*: 16.0 Hz, 1H, α-H), 7.69 (d, *J*: 16.0 Hz, 1H, β-H), ar-H: [7.47-7.51 (m, 2H), 7.33-7.37 (m, 2H), 6.99-6.88 (m, 4H)], 3.88, 3.83 (s, 6H, -OCH_3,), ^{13}C-NMR (100 MHz, DMSO-d_6): 160.38 (-C=NOH), 117.77 (α-C), 134.58 (β-C), ar-C [157.61(C), 157.87(C), 130.54 (CH), 130.54 (CH), 130.24 (CH), 128.74 (CH), 127.45(C), 127.64 (CH), 125.35 (C), 113.81 (CH), 113.72 (CH), 110.98 (CH)], 55.58, 55.42, [-OCH_3]. LC/ MS : (m/z) (%) [M+1]: 268 (100). Anal. calcd for $C_{17}H_{17}NO_3$ (m.w.: 283): C, 72.07; H, 6.05; N, 4.94.

Found: C, 72.12; H, 5.98; N, 5.03. LC-MS: (*m/z*) % $[M+K-H]^+$: 321(100), $[M+K]^+$: 322(13), $[M+Na+H_2O+H]^+$: 325(50).

*(1E,2E)-3-(3-methoxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one oxime (**2g**):* Yield: 74%, white solid, R_f = 0.59 (*n*-hexane-diethyl ether, 1:3), m.p.(°C): 113-114, UV-vis λ nm (logϵ): 284.41(0.96), IR (KBr, cm^{-1}): 3160 (=NOH), 1603 (-C=N), 1578 (-C=C-olefinic), 1513, 1440 (-C=C-aromatic) , ^{1}H-NMR (400 MHz, DMSO-d_6): 6.55 (d, *J*: 15.6 Hz, 1H, α-H), 7.68 (d, *J*: 15.6 Hz, 1H, β-H), ar-H: [7.47-7.51 (m, 2H), 7.36-7.27 (m, 1H), 6.99-6.86 (m, 5H)], 3.89, 3.84 (s, 6H, -OCH_3,), ^{13}C-NMR (100 MHz, DMSO-d_6): 160.47 (-C=NOH), 117.66 (α-C), 139.49 (β-C), ar-C [159.89 (C), 157.33 (C), 130.50 (CH), 137.52 (C), 130.54 (CH), 130.24 (CH), 129.72 (CH), 120.27 (CH), 126.52 (C), 113.83 (CH), 113.91 (CH), 112.30 (CH)], 55.58, 55.42, [-OCH_3]. LC/ MS : (m/z) (%) [M+1]: 268 (100). Anal. calcd for $C_{17}H_{17}NO_3$ (m.w.: 283): C, 72.07; H, 6.05; N, 4.94. Found: C, 71.94; H, 5.96; N, 5.05. LC-MS: (*m/z*) (%) $[M-OH]^+$: 266(85), [M+1]: 284(40).

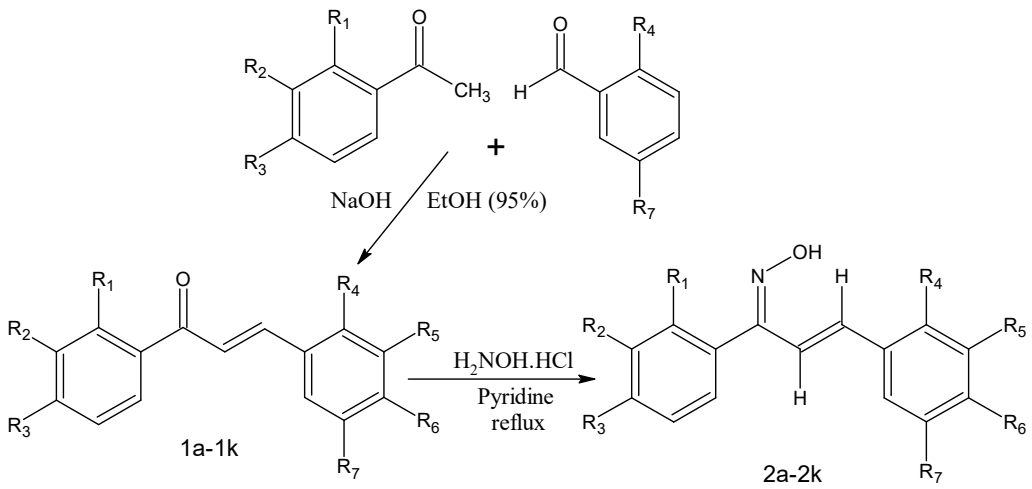
*(1E,2E)-3-(2,3-dimethoxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one oxime (**2h**):* Yield: 73%, white solid, R_f = 0.72 (*n*-hexane-diethyl ether, 1:3), m.p.(°C): 116-118, UV-vis λ nm (logϵ): 305.57 (1.21), 326.14 (1.19), IR (KBr, cm^{-1}): 3152 (=NOH), 1606 (C=N), 1576 (-C=C-olefinic), 1514, 1442 (-C=C-aromatic), ^{1}H-NMR (400 MHz, DMSO-d_6): 11.54 (s, 1H, =NOH), 6.98 (d, *J*: 16.8 Hz, 1H, α-H), 7.67 (d, *J*: 16.8 Hz, 1H, β-H), ar-H: [7.35-7.29 (m, 2H), 7,12-7,08 (m, 3H) 7.02 (d, *J*: 8.0 Hz, 2H)], 3.41, 3.56, 3.62 (s, 9H, OCH_3), ^{13}C-NMR (100 MHz, DMSO-d_6): 160.16 (-C=NOH), 118.31 (α-C), 131.40 (β-C), ar-C [157.00 (C), 155.64 (C), 147.44 (C), 130.25 (2CH), 128.62 (C), 128.42 (C), 124.66 (CH), 119.25 (CH), 124.66 (CH), 114.20 (2CH)], 61.08, 56.13, 55.62, [-OCH_3]. Anal. calcd for $C_{18}H_{19}NO_4$ (m.w.: 313): C, 68.99; H, 6.11; N, 4.47. Found: C, 68.90; H, 6.27; N, 4.58. LC-MS: (*m/z*) (%) $[M+1]^+$: 314 (100), $[M+Na]^+$: 336(55).

*(1E,2E)-3-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one oxime (**2i**):* Yield: 74%, white solid, R_f = 0.66 (*n*-hexane-diethyl ether, 1:3), m.p.(°C): 148-149, UV-vis λ nm (logϵ): 245.30 (0.98), 312.12 (1.21), IR (KBr, cm^{-1}): 3151 (=NOH), 1606 (-C=C-olefinic), 1579 (-C=C-aromatic), ^{1}H-NMR (400 MHz, DMSO-d_6) : 6.96 (d, *J*: 16.0 Hz, 1H, α-H), 7.59 (d, *J*: 16.0 Hz,1H, β-H), ar-H: [7.42-7.45 (m, 2H), 7.49-7.51 (m, 3H), 6.93-6.97 (m, 2H)], 3.80, 3.84, 3.87 (s, 9H, -OCH_3,), ^{13}C-NMR (100 MHz, DMSO-d_6): 161.75 (-C=NOH), 115.53 (α-C), 134.40 (β-C), ar-C [160.28 (C), 158.92 (C), 158,16 (C), 130.72 (CH), 130.57 (CH), 128.74 (CH), 127.66 (C), 118.48 (C), 113.74 (CH), 113.69 (CH), 98.47 (CH), 106.12 (CH)], 55.48, 55.42, 55.31[-OCH_3]. Anal. calcd for $C_{18}H_{19}NO_4$ (m.w.: 313): C, 68.99; H, 6.11; N, 4.47. Found: C, 68.92; H, 6.21; N, 4.43. LC-MS: (*m/z*) (%) $[M-OH]^+$: 296(100), $[M+H]^+$: 314(90).

*(1E,2E)-1-(4-methoxyphenyl)-3-(2,4,5-trimethoxyphenyl)prop-2-en-1-one oxime (**2j**):* Yield: 66%, white solid, R_f =0.63 (*n*-hexane-diethyl ether, 1:3), m.p.(°C): 160-162, UV-vis λ nm (logϵ): 285.20 (1.52), 294.28 (1.42), 349.01 (1.68), IR (KBr,cm^1): 3157 (=NOH), 1604 (C=N), 1568 (-C=C-olefinic), 1510, 1436 (-C=C-aromatic), ^{1}H-NMR (400 MHz, DMSO-d_6) : 11.34 (s, 1H, =NOH), 6.65 (d, *J*: 16.0 Hz, 1H, α-H), 7.60 (d, *J*: 16.0 Hz, 1H, β-H), ar-H: [7.58-7.62 (m, 2H), 7.15-7.17 (m, 1H), 6.98-7.03 (m, 2H), 6.67-6.68 (m, 1H)], 3.68, 3.73, 3.81, 3.83 (s, 12H, -OCH_3,), ^{13}C-NMR (100 MHz, DMSO-d_6): 160.03 (-C=NOH), 116.19 (α-C), 131.64 (β-C), ar-C [156.13 (C), 157.47 (C), 152.66 (C), 151.87 (C), 130.55 (2CH), 130.52 (C), 116.16 (C), 114.15 (2CH), 110.47 (CH), 98.43 (CH).], 55.54, 56.19, 56.64, 56.76 (-OCH_3). Anal. calcd for $C_{19}H_{21}NO_5$ (m.w.: 343): C, 66.46; H, 6.16; N, 4.08. Found: C, 66.56 ; H, 6.19; N, 4.12. LC-MS: (*m/z*) (%) $[M+H_2O-1]^+$: 360(100).

*(1E,2E)-1-(4-methoxyphenyl)-3-(2,3,4-trimethoxyphenyl)prop-2-en-1-one oxime (**2k**):* Yield: 67%, white solid, R_f = 0.74 (*n*-hexane-diethyl ether, 1:3), m.p.(°C): 139-140, UV UV-vis λ nm (logϵ): 246.30 (0.62), 312.12 (0.82), IR (KBr, cm^{-1}): 3149 (=NOH), 1601 (-C=N), 1598 (-C=C-olefinic), 1493 (-C=C-aromatic), ^{1}H-NMR (400 MHz, DMSO-d_6) : 11.34 (s, 1H, =NOH), 6.87 (d, *J*: 16.0 Hz, 1H, α-H), 7.49 (d, *J*: 16.0 Hz, 1H, β-H), ar-H: [7.40-7.43 (m, 3H), 7.01 (d, 2H), 6.81-6.84 (m, 1H)], 3.68, 3.73, 3.81, 3.83 (s, 12H, OCH_3,),^{13}C-NMR (100 MHz, DMSO-d_6):160.09 (-C=NOH), 117.19 (α-C), 131.53 (β-C), ar-C [154.57 (C), 155.86 (C), 152.22 (C), 142.34 (C), 130.49 (2CH), 128.28 (C), 123.06

(C), 121.89 (CH), 114.16 (2CH), 109.09 (CH)], 55.63, 56.41, 60.89, 61.67 (-OCH_3) . Anal. calcd for $C_{19}H_{21}NO_5$ (m.w.: 343): C, 66.46; H, 6.16; N, 4.08. Found: C, 66.57 ; H, 6.21; N, 4.03. LC-MS: (*m/z*) (%) $[M+Na]^+$: 366 (100), $[M+Na+H]^+$: 367(60).



Comp.	R_1	R_2	R_3	R_4	R_5	R_6	R_7
1a, 2a	-H	-OH	-H	-H	-H	-H	-H
1b, 2b	-H	-H	-OH	-H	-H	-H	-H
1c, 2c	-OCH_3	-H	-H	-OCH_3	-H	-H	-H
1d, 2d	-OCH_3	-H	-H	-OCH_3	-OCH_3	-H	-H
1e, 2e	-OCH_3	-H	-H	-OCH_3	-OCH_3	-OCH_3	-H
1f, 2f	-H	-H	-OCH_3	-OCH_3	-H	-H	-H
1g, 2g	-H	-H	-OCH_3	-H	-OCH_3	-H	-H
1h, 2h	-H	-H	-OCH_3	-OCH_3	-OCH_3	-H	-H
1i, 2i	-H	-H	-OCH_3	-OCH_3	-H	-OCH_3	-H
1j, 2j	-H	-H	-OCH_3	-OCH_3	-H	-OCH_3	-OCH_3
1k, 2k	-H	-H	-OCH_3	-OCH_3	-OCH_3	-OCH_3	-H

Scheme 1. Synthesis of chalcone oximes (**2a-2k**) from chalcones (**1a-1k**).

2.3. α-Glucosidase Inhibition Assay

α-Glucosidase inhibition assay was performed spectrophotometrically. α-Glucosidase from *Saccharomyces cerevisiae* (Sigma-Aldrich) was dissolved in phosphate buffer (pH 6.8, 50 mM). Test compounds were dissolved in DMSO. In 96-well microtiter plates, 20 µL of test sample, 20 µL of enzyme (20 mU/mL) and 135 µL of buffer were added and incubated for 15 minutes at 37 °C. After incubation, 25 µL of *p*-nitrophenyl-α-D-glucopyranoside (2 mM, Sigma Aldrich) was added and change in absorbance was monitored for 30 minutes at 400 nm. Test compound was replaced by DMSO (7.5% final) as control. Acarbose (Sigma-Aldrich) was used as a standard inhibitor.[35-39]

3. Result and Discussion

3.1. Synthesis

In this work, due to the biological evaluation, known hydroxy and methoxy substituted chalcones[19,24-31] (**1a-1k**) have been prepared by the Claisen–Schmidt condensation reaction by using substituted acetophenone and benzaldehyde[32-33] (Scheme 1), then a new series of chalcone oximes (**2a-2k**) were synthesized from corresponding chalcones (**1a-1k**) and hydroxyl amine hydrochloride at

reflux temperature using pyridine as solvent in the range of 66-81% yield, respectively (scheme 1). The crude products were purified with column chromatography.

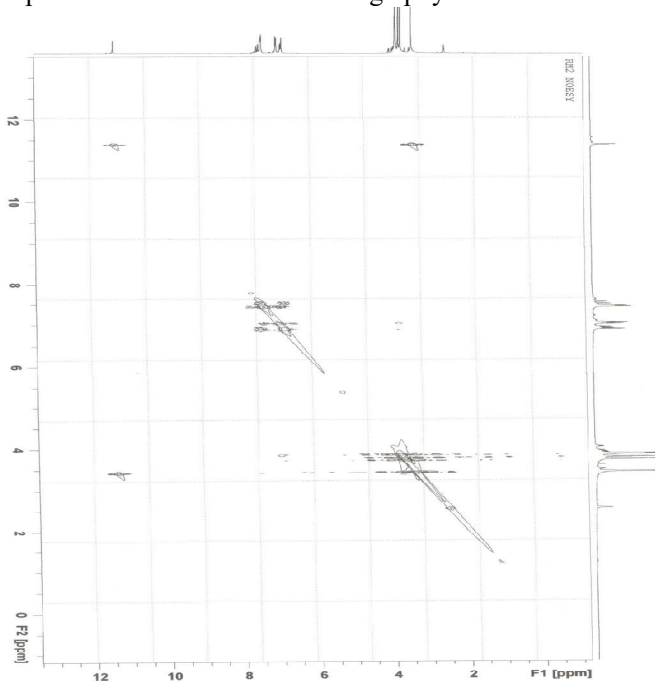


Figure 1. NOESY spectrum of compound **2k**, DMSO-d_6, 400 MHz NMR.

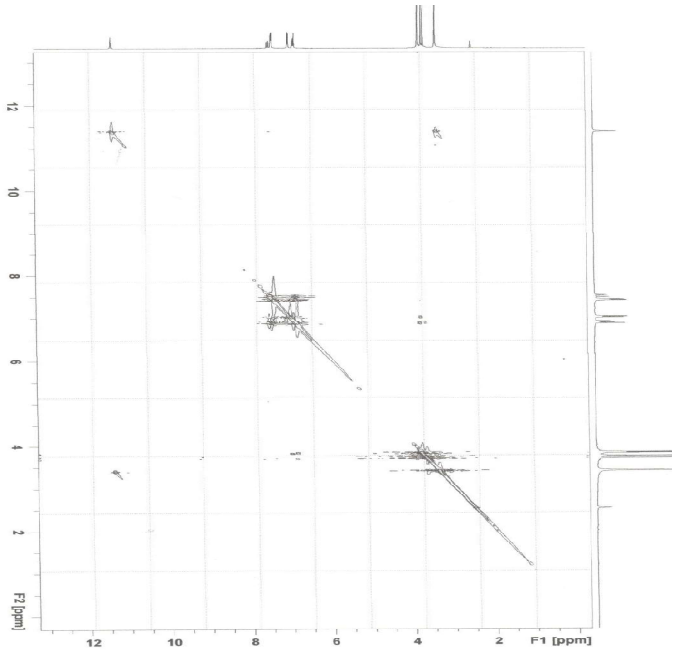


Figure 2. ROESY spectrum of compound **2k**, DMSO-d_6, 400 MHz NMR.

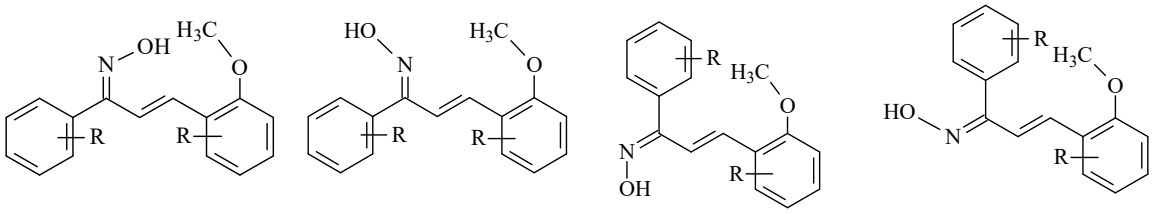
All the synthesized compounds (**2a-2k**) were characterized using spectroscopic techniques such as 1D-NMR: ^{1}H, ^{13}C/APT/DEPT and 2D-NMR: ^{1}H-^{1}H COSY, NOESY and ROESY, UV-Vis, FT-IR, LC-MS, elemental analyses and by the help of ACD NMR program. The mass spectra of chalcone oximes (**2a-2k)** showed molecular ion peaks at the appropriate *m*/*z* values which are given in experimental part, respectively. The ^{1}H and ^{13}C NMR spectra of compounds **2a-2k**, in particular, =NOH showed peaks at within the range of δ_H 11.02-11.48 (1H, bs) and C_1 at δ_C 158.0 ppm, which are

an indication of oxime group of chalcone. Also, the -OH moiety of products **2a-2b** exhibited characteristic signals at δ_H 9.7-9.8 ppm in the ^{1}H NMR, respectively. The most noticeable feature for the structural characterization of chalcone oximes is the assignment of the proton resonances of the α,β-unsaturated moiety within the range of δ 6.55-6.98 ppm and δ 7.45-7.76 ppm with 15.6/16.0/16.4/16.8 Hz coupling constant, respectively which showed the stereochemistry of -CH=CH- in *E* configuration. Structural elucidation for the geometry of chalcone oxime compounds was supported by a 2D NOESY (Figure 1) and ROESY (Figure 2) NMR spectra.[40] Here is the NOESY and ROESY spectra of compound **2k** showed a spatial interaction between oxime -OH with -OCH_3 at C-2 position of B ring and β-H of the chalcone oxime compounds. Similar results were obtained for the other compounds. Therefore, geometry of compounds **2a-2k** is assigned as 1*E*,2*E*-isomer in *cisoid* form.

In the literature, 1*Z*,2*E* geometry of compounds **2g** and **2j** have mentioned.[23] Moreover, their melting points were reported as 30 °C and 95 °C, respectively. In our case, melting points of compounds **2g** and **2j** were found to be 113-114 °C (**2g**) and 160-162 °C (**2j**). These data clearly showed that compounds **2g** and **2j** were two different geometrical isomer (1*Z*,2*E*- /1*E*,2*E*-) to each other. FT-IR spectrum of **2a-2k** showed characteristic band of =NOH and -OH at ~ 3165 and 3285 cm^{-1}, and imine group (-C=N) at 1635-1658 cm^{-1}, respectively.

*3.2. Theoretical Calculation of Compounds **2a-2k***

The formation of the chalcone oxime can exist as geometric *E*/*Z*-isomers with four possible *cisoid* and *transoid* form (Figure 3).



1*E*,2*E* (*cisoid* form) 1*Z*,2*E* (*cisoid* form) 1*E*,2*E* (*transoid* form) 1*Z*,2*E* (*transoid* form)

Figure 3. The possible geometric isomer of the chalcone oxime compounds (**2a-2k**).

Table 1. Calculated energy for the geometrical isomers of compounds **2a-2k** (PM3)

Compounds	Conformation (1*Z*,2*E*) (kcal/mol)		Conformation (1*E*,2*E*) (kcal/mol)	
	transoid	*cisoid*	*transoid*	*cisoid*
2a	31.05	30.94	31.10	28.98
2b	28.99	28.34	33.36	28.33
2c	7.40	6.58	8.87	6.24
2d	-32.06	-30.01	-30.68	-32.42
2e	-31.65	-33.45	-30.46	-33.46
2f	-29.86	-28.84	-29.22	-30.01
2g	-32.26	-30.27	-31.34	-32.33
2h	-34.54	-32.57	-33.11	-35.04
2i	-34.47	-33.44	-36.06	-38.85
2j	-85.02	-80.95	-70.01	-85.82
2k	-68.04	-68.22	-69.78	-70.91

Theoretical calculations were performed with HYPERCHEM 7.5 program on an HP PC intel core i5 computer. The molecular structures for the conformation of compounds **2a-2k** were optimized with PM3 method.[20-22]. In the main skeletal structure of the molecules, conformational analyzes were performed over the six different torsional angel. An average of 120 conformation of each isomer was

detected and the results are given in Table 1. The theoretical calculations of compounds **2a-2k** showed that *cisoid* 1*E*,2*E* is the most stable form of all for the compounds **2a-2k**. In the literature, the synthesis of different chalcone oxime compounds resulted 1*Z*,2*E* and 1*E*,2*E* geometrical isomers.[23,34-37,41] This could be due to the experimental condition which were used for the synthesis of chalcone oxime compounds.

*3.3. α-Glucosidase Inhibitory Activity of Compounds **2a-2k***

Synthesized chalcone oximes (**2a-2k**) were subjected to α-glucosidase inhibition assay against acarbose.[38-41] The IC_{50} values of substituted chalcone oximes (**2a-2k**) were listed in Table 2, and IC_{50} values of all these compounds were determined by interpolation of the dose-response curves and given as means of three experiments. No significant inhibitory effect was detected for compound **2j** and IC_{50} values of compounds **2i-2k** were not determined. Among the tested compounds, **2a** and **2b** showed the most significant α-glucosidase inhibition activity by 51.52±1.09% and 47.24±6.08% at a concentration of 10 µM, respectively (Table 2). Acarbose, known *α*-glucosidase inhibitor used as anti-diabetic drug, showed inhibitory effect by 43.27±1.91% at the same concentration. Compound **2a** and **2b** IC_{50} values were calculated as 1.61±0.16 µM and 3.36±0.58 µM, respectively.

Table 2. *α*-Glucosidase inhibition of synthesized chalcone oximes (**2a-2k**) (IC_{50}, µM).

Compounds	Inhibition % ± SD (10 µM)	IC_{50} (µM) ± SD
2a	51.52 ± 1.09	1.61 ± 0.16
2b	47.24 ± 6.08	3.36 ± 0.58
2c	47.84 ± 9.18	11.26 ± 2.04
2d	40.82 ± 7.26	9.20 ± 2.90
2e	63.65 ± 4.34	9.39 ± 0.94
2f	20.06 ± 6.14	12.58 ± 0.98
2g	25.59 ± 3.98	14.00 ± 2.00
2h	56.71 ± 4.15	25.55 ± 0.38
2i	52.02 ± 8.17	nd
2j	ni	nd
2k	26.31 ± 2.60	nd
Acarbose[a]	43.27 ± 1.91	13.34 ± 1.26

ni: no inhibition, nd: Not determined, [a]Reference compound

Synthesized new chalcone oxime compounds **2a** and **2b** have substantial inhibition potential against the acarbose. When the methoxy is oriented at the *ortho* position of ring A of chalcone oximes, the number of methoxy substitution increased, α-glucosidase inhibition activity of compounds **2c-2e** increased with the IC_{50} values of 11.26 and 9.20 µM, respectively. Whereas, methoxy is substituted at the *para* positon of ring A of chalcone oximes, even increasing the number of methoxy substitution, α-glucosidase inhibition activity of compounds **2f-2l** decreased. Therefore, these result showed that the methoxy is at the *ortho* position of ring A is more effective than *para* position of chalcone oximes compounds for the α-glucosidase inhibition activity. This result showed that the number of methoxy group might be an important effecting factor of inhibitory activities. When the methoxy group at the 3-position of benzene ring (A) might be beneficial to improve this kind of compounds inhibitory activities that could be related to the lipophilicity. But, chalcone oxime (**2a**) had –OH at the *meta* positon of ring A gave the most IC_{50} value as 1.61±0.16 µM (Table 2 and Figure 4). The *α*-glucosidase inhibition activity indicated that chalcone oxime having hydroxyl group are more active than the chalcone oxime having methoxy group. Dose-dependent inhibitory effect of compounds **2a** and **2b** is shown in figure 4.

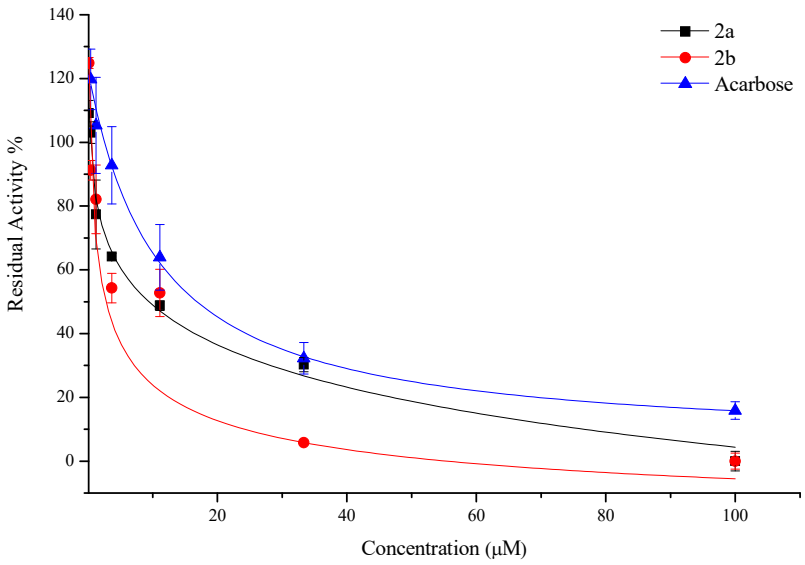


Figure 4. Dose-dependent inhibitory effect of compounds **2a** and **2b**. Acarbose was used as standard inhibitor. Inhibitory effect of the tested compounds and Acarbose was measured at the range of 0.045–100 μM concentrations. Residual activities of the compounds were expressed as the mean ± S.D., measured in triplicate.

In the literature various substituted chalcone compounds such as; sulfonamide chalcone,[42-43] 3',5'-digeranylated chalcone,[44] aminochalcones,[42] and the other substituted chalcone compounds[42, 45] were mentioned to be potent inhibitor against α-glucosidase. In our case, screening of the hydroxyl and methoxy substituted chalcone oximes compounds (**2a-2k**) against α-glucosidase revealed that hydroxyl substituted chalcone oximes **2a** and **2b** were found to be the best inhibitor against *α*-glucosidase activity.

4. Conclusion

In summary, a two-step procedure for the synthesis of new hydroxyl and methoxy substituted chalcone oximes (**2a-2k**) from chalcone and hydroxylamine hydrochloride has been demonstrated. Synthetic chalcone oximes are very useful reactive intermediates for the efficient construction of various *N*-heterocycles and should be evaluated for their potential use of new bioactive chalcone oxime derivatives. Our results showed that most of compounds exhibited potent inhibition on α-glucosidase inhibitory activity with IC_{50} values in the range of 1.61-25.55 μM. Specifically, compounds bearing -OH (**2a-2b**) showed more potent inhibitory activities than the other compounds. In addition, compounds **2a-2b** and **2c-2g** demonstrated more potent inhibitory activity (1.61-12.58 μM) than the reference standard inhibitor acarbose with IC_{50} value of 13.34 μM. Thus, most of the products exhibit good α-glucosidase inhibition activity. Thus, compounds **2a**, **2b**, **2e**, **2d**, **2c**, **2f** and **2g** would be useful for the development of new drugs such as antidiabetics.

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Supporting Information

Supporting information accompanies this paper on http://www.acgpbus.org/OC

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